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10/09/02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of **MALCOLM KING**)
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)
Serial No. **09/645, 594**) Examiner: **Lauren Q. Wells**
)
Filed: **August 25, 2000**) Group Art Unit: **1619**
)
For:**Use Of Charged Dextran as**)
a Mucoactive Agent and Methods And)
Pharmaceutical Agents Relating)
Thereto)

The Commissioner of Patents
& Trademarks
Washington, D.C. 20231
U.S.A.

Dear Sir:

DECLARATION UNDER 37 CFR §1.132 OF (DR. DAVID P. SPEERT)

I, David Speert, a citizen of Canada, residing at 4616 W. 2nd Avenue, Vancouver, British Columbia, Canada, DO HEREBY DECLARE AND SAY:

1. I am professor, academic researcher and medical physician in the Department of Pediatrics at the University of British Columbia, Vancouver, Canada.

2. I am active in numerous scientific professional associations. A list of my memberships is provided in my *curriculum vitae* attached as Exhibit A hereto.

3. I have been conducting research in the field of Pediatric Infectious Diseases since 1980. I have authored or coauthored over 120 publications in the field of Pediatric Infectious Diseases which have been published in refereed journals, or included in conference proceedings. A more complete listing of my publications is provided in my *curriculum vitae* attached as Exhibit A hereto.

4. I have read and understood the specification of U.S. Patent Application Serial No 09/645,594 ('594) that was shown to me by patent counsel.

"DECREASING" and "IMPROVING"

5. I have read and understood the claims of the '594 patent application. It was clear to me what was meant by the phrases "decreasing viscoelasticity of respiratory tract mucus" and "improving mucus clearance". It is recognized that mucus is a normal constituent of the endobronchial space and that inhibition of the capacity to remove respiratory tract mucus (e.g. by such maneuvers as coughing) is deleterious to one's health.

6. In the art, the phrase "decreasing vicoelasticity of respiratory tract mucus" means diminishing the capacity of mucus material from the lung airways to stretch and to form string-like structures (Feng, W., et al., Am J. Resp. Crit. Care Med. ***157***:710-714, 1998). It is known in the art, that one could determine or assess changes in the viscosity of respiratory tract mucus by a number of methods, such as done in the '594 patent application at page 14 under the heading "Mucus Viscoelasticity Measurements". One can take measurements before, and after administration of the charged dextran to determine the change in viscoelasticity of the mucus.

7. In the art the phrase "improving mucus clearance" means enhancing the capacity of airway mucus to be removed from the lungs (Feng, W., et al., Am J. Resp. Crit. Care Med. ***157***:710-714, 1998), One of skill in the art would know that this could be determined or assessed by a number of methods, such as disclosed in the '594 patent application at page 18, in the paragraph where it is states that decrease in mucus rigidity index is consistent with enhanced mucus clearability by ciliary and cough mechanisms and references are referred to. The term "impaired mucus clearance would have a corresponding converse meaning to that of "improving mucus clearance"..

The '594 Patent Application

8. The '594 patent application describes the use of a low molecular weight (e.g. 500 – 5000 dalton) charged dextran (dextran sulfate) to decrease the viscoelasticity and improve mucus clearability in a patient. The '594 patent application uses the dextran sulfate to alter the rheology of respiratory tract mucus and thereby enhance its clearability from the lung. In cystic fibrosis and other chronic respiratory tract conditions, lung infection and injury appears to be enhanced because mucus is abnormally viscous and cannot be readily removed from the airways. The '594 patent application discloses a solution to this problem using dextran sulfate. The use of dextran sulfate in the '594 patent application is distinct from that of the other references I have reviewed and listed herein below.

PRIOR ART

9. I have read and understood the following references:

(a) United States Patent No. 5,514,665 to Speert et al;

(b) Beller et. al., "Biochemical identification Of The Mucus Of *Pseudomyxoma Peritonei* As The Basis For Mucolytic Treatment", Am. J. Obstet Gynecol 1986; 155-970

(c) United States Patent No. 5,980,865 to Ahmed

(d) WO 91/15216 to Kennedy et al.

10. I am a co-inventor on United States Patent No. 5,514,665. This patent teaches that dextrans interfere with adhesion of bacteria (particularly *Pseudomonas aeruginosa*) to epithelial cells. The patent does not teach anything about effects of dextrans on mucus clearance, mucus viscoelastisity or methods of diagnosing and methods of determining dosage. My patent is for a purpose totally distinct from that of Dr. King's '594 patent application. Attachment of bacteria to epithelial cells is thought to be the first step in infection, particularly in the respiratory tract. In conditions such as cystic fibrosis, bacteria such as *P. aeruginosa* appear to have enhanced capacity to attach and thereby cause disease. My patent protects the observation that this enhanced

attachment may be attenuated with dextrans. This use is quite distinct from that of the use described in Dr. King's '594 patent application. He proposes to use dextran sulfate to alter the rheology of mucus and thereby enhance is clearability from the lung. In cystic fibrosis and other chronic respiratory tract conditions, lung infection and injury appears to be enhanced because mucus is abnormally viscous and cannot be readily removed from the airways. Dr. King's '594 patent application teaches that dextran sulfate can correct this problem and proposes a mechanism of action altogether distinct from that in my patent and results in a different medical application for dextran sulfate.

11. In my opinion Beller et al., discloses the biochemical identification of the "gelatinous material" (referred to as "mucus" in the paper) of *pseudomyxoma peritonei* and the use of dextran sulfate to lyse the mucus in two patients with psudomyxoma. The mucus was characterized by the authors and found to be 98% protein and only 2-5% carbohydrate. This mucus is quite different from that of the respiratory tract which is predominantly carbohydrate (approximately 80% carbohydrate, 20% protein by weight, containing the sugars galactose, N-acetylgalactosamine, N-actylglucosamine, fructose and sialic acid). The patients in Beller received either 10% or 5% dextran sulfate but the molecular weight was not described. Beller's use and the nature of the mucus lysed by the dextran sulfate are quite distinct from that described in Dr. King's '594 patent application. The mechanism of action is not known from Beller's observation and it is my opinion that one cannot predict that there would be an analogous effect on mucus from another anatomical site with an altogether different chemical composition.

12. In Ahmed the use of 0.005 – 1 mg/kg of ultra low molecular weight heparins or other sulfated polysaccharides of molecular weight 1000 – 3000 Daltons are taught in the use as an anti-inflammatory agent to treat allergic diseases of the respiratory tract. There is no mention in Ahmed of mucus or use of such agents as a mucoactive agent or to decrease mucus viscoelasticity or increase clearability of respiratory tract mucus. Ahmed's use of dextran sulfate is altogether different from that in the '594 patent application that teaches use of dextran sulfate to alter mucus rheology and enhance

mucus clearability. It is my opinion that one could not infer that an agent useful to treat allergic diseases or inflammatory conditions could also be used to alter mucus rheology.

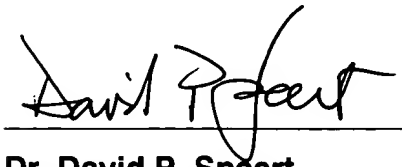
13. WO 91/15216 to Kennedy teaches that dextran sulfate has anti-elastase activity and can be used in conditions where there is enhanced elastolytic activity in the respiratory tract. Elastase has proteolytic activity and enhances colonization of bacteria. Inhibiting elastase activity results in inhibition of the development of colonization sites for bacteria. There is no mention in Kennedy of respiratory tract mucus. This use is altogether different from that taught by the '594 patent application. The dextran sulfate in Kennedy is not used as a mucolytic or mucokinetic agent. On the other hand in the '594 patent application the dextran sulfate acts directly on the rheology of respiratory tract mucus and interferes with the structure thereof.

14. It is my opinion that one of skilled in the art, in light of the references noted above would not have known that dextran sulfate (or a charged dextran) could be used to decrease the viscoelasticity or improve respiratory tract mucus clearability from the lung through mucolytic and/or mucokinetic effects.

15. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statement

and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or patent resulting therefrom.

Signed this 18th day of September, 2002



Dr. David P. Speert